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Anxiety and depression following cumulative low-level exposure to organophosphate pesticides.

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Abstract

Previous research suggests that individuals with a prior history of pesticide poisoning are at increased risk of psychiatric disorder (Freire & Koifman, 2013), but findings regarding the impact of cumulative low-level exposure are inconsistent. The aim of the current study was to investigate whether sheep farmers with a history of low-level exposure to organophosphate pesticides (1) report a higher level of psychological distress on subjective symptom questionnaires, compared to unexposed controls (2) also meet internationally agreed diagnostic criteria for a psychiatric disorder more often than unexposed controls. 127 sheep farmers were evaluated and compared to 78 unexposed controls, matched in terms of gender, education, level of intelligence, working status and area of residence. Both self-report measures and structured clinical interviews were used to assess mental health. The exposed cohort reported significantly higher rates of anxiety and depression when self-report questionnaires were used to evaluate mood, even when stressful life events, demographic and physical health factors were taken into account. However, when diagnostic interviews were used to assess mood, this pattern only held true for anxiety.

1. Introduction

Anxiety and depression are common mental health conditions affecting millions of people around the world. The Psychiatric Morbidity Survey in 2007 estimated 2.28 million people in the UK were suffering from anxiety disorders and 1.24 million people were suffering from depression (McManus, Meltzer, Brugha, Bebbington & Jenkins, 2009). These figures are projected to rise over the next two decades (McCrone, Dhanasiri, Patel, Knapp & Lawton-Smith, 2008). A number of factors have been implicated in the onset and course of these conditions including biological, psychological and social factors. The rate of depression seen in women from western industrialised nations is twice that of men (Patel, 2005) and the reason for this disparity has been much debated. Additionally, individuals who are unemployed, of low socio-economic status, or who have suffered stressful life events are thought to be at increased risk of developing depression (Brown & Harris, 1978; 1986). Disturbances in neurotransmitter functioning and genetic factors have also been implicated in the aetiology of anxiety disorders and depression (Marchand, Dilda & Jensen, 2005).

Epidemiological studies have also reported higher incidences of anxiety and depression in particular groups of individuals such as those with chronic health conditions (NICE clinical guideline 91, 2009) and individuals in specific occupations. With regard to the latter, Roberts and Lee (1993) found the highest incidence of depression in farming, fishing and forestry occupations. This was confirmed by a study by Sanne, Mykletun, Dahl, Moen and Tell, (2003) who found male agricultural workers had the highest incidence of anxiety and depression compared to other

occupational groups. Additionally, Gregoire (2002) found farmers account for the largest number of suicides amongst other occupational groups in the United Kingdom (UK) and that suicide is the second most common cause of death in UK farmers after accidents.

The reason behind the elevated risk of mood disorder in farming populations is unclear. Some researchers have reported a link between exposure to pesticides, mood disorder and suicidal behaviour (e.g. Amr, Halim & Moussa, 1997; Beard, Umbach, Hoppin, Richards, Alavanja, Blair, Sandler & Kamel, 2011; 2014; Beseler & Stallones, 2008; Lee et al, 2007; Levin et al, 1976; Mackenzie Ross, Brewin, Curran, Furlong, Abraham-Smith & Harrison, 2010; Meyer, Koifman, Koifman, Moreira, de Rezende, Chrisman & Abreu-Villaca, 2010; Parron et al, 1996; Roldan-Tapia, Nieto-Escamez, del Aguila, Laynez, Parron & Sanchez-Santed, 2006; Salvi, Lara, Ghisolfi, Portela, Dias, & Souza, 2003; Stallones, 2006; Steenland, Dick, Howell, Chrislip, Hines, Reid, Lehman, Laber, Krieg Jr & Knott, 2000; Stephens, Spurgeon, Calvert, Beach, Levy, Berry & Harrington, 1995; van Wijngaarden 2003; Zhang et al, 2009). Organophosphate pesticides (OPs) in particular are associated with an elevated risk of neuropsychiatric disorder (e.g. Wesseling, van Wendel de Joode, Keifer, London, Mergler, & Stallones, 2010). They are the most widely used group of pesticides in the world and are considered by the World Health Organisation (WHO) to be one of the most hazardous pesticides to vertebrate animals, responsible for many cases of poisoning worldwide, particularly in developing countries where protective measures are lacking (WHO report, 1990; De Silva, Samarawickrema & Wickremasinghe, 2006). The neurotoxic effects of high level acute poisoning are well established and involve inhibition of the enzyme acetylcholinesterase (AChE) causing

changes in peripheral, autonomic and central nervous system function (the cholinergic crisis) resulting in a constellation of physical, cognitive and psychiatric symptoms. However; OPs disrupt many other neurotransmitters and some of these are involved in mood regulation such as serotonin (Aldridge, Levin, Seidler, & Slotkin, 2005; Slotkin, Levin & Seidler, 2006). This could explain the link between pesticide exposure and mood disorder observed in earlier studies.

This association appears strongest in individuals who report previous instances of acute poisonings (Beseler & Stallones, 2008; Beseler et al 2006; 2008). However, the impact of long-term low-level exposure to OPs (in doses below that causing acute toxicity) on human health is less clear. Some studies have found evidence of ill health, mood disorder and cognitive impairment following low-level exposure to OPs whilst others have not (see reviews by Freire & Koifman, 2013 and Mackenzie Ross, McManus, Harrison & Mason, 2013). These inconsistencies may be the result of methodological differences that exist between the different studies in this field. For example, studies investigating this issue have used a plethora of different methods to explore the role of exposure, investigating different occupational groups with differing levels of contact with OPs, routes and nature of exposure, use of protective clothing, demographic and geographic profiles, and over a wide variety of time frames. What's more, they tend to use different definitions and measures of exposure, further complicated by the fact that there is currently no consensus in the literature over what constitutes acute or chronic exposure. Finally, objective measures of exposure are seldom available making it difficult to establish clear dose-response relationships.

Difficulties also exist when it comes to measuring mood. Methods that have been used to assess the presence of mood disorder in OP exposed populations range from simply asking participants whether or not they have ever been diagnosed with depression/anxiety by a physician (e.g. Beard et al, 2014) to asking participants to complete standardised symptom questionnaires with differing degrees of sensitivity and specificity (e.g. Ames et al, 1995; Farahat et al, 2003; Jamal et al, 2002; Mackenzie Ross et al, 2007; 2010; Roldan-Tapia et al, 2006; Stallones and Beseler, 2002a; Steenland et al, 2000; Stephens et al, 1995). Although self-report measures may be useful for screening purposes in large populations, it is not always clear whether findings are comparable with what would be derived from structured clinical interviews undertaken by mental health professionals using internationally agreed diagnostic criteria for mental disorders. Indeed, previous research with other patient cohorts (including multiple sclerosis, cancer, cardiomyopathy, hepatitis C) has shown that self-report measures may not be good indicators of psychiatric disorder (Golden et al, 2007; Mitchell et al, 2010; Poole et al, 2006; Watson et al, 2014), and a recent study suggests this may be particularly true for research with OP exposed groups (Harrison & Mackenzie Ross, under review). Structured interviews standardise the coverage of specific psychiatric issues (thus reducing the possibility of missed diagnoses) and require the systematic appraisal of relevant symptoms, to reduce misdiagnosis. As such, clinical interviews are considered the ‘gold standard’ for diagnosis.

In the last two decades, only two published studies report evaluations of OP exposed participants using strict diagnostic criteria. First, Amr et al (1997) examined 208 Egyptian pesticide formulators, 172 pesticide applicators and 223 control subjects. All

underwent a full psychiatric interview and diagnoses were made in accordance with the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-III-R).

Psychiatric disorders were found to be more common in exposed subjects, particularly depression and dysthymic disorder. However, as the authors did not collect in-depth information about participants' exposure history, it is impossible to determine whether this is related to long-term low-level exposure, as the possibility of historic acute poisonings cannot be ruled out.

Second, Salvi et al (2003) assessed 37 tobacco workers from Brazil who had been exposed to organophosphate pesticides, evaluating them shortly after exposure and then again, following 3 months without exposure. Diagnoses were made in accordance with the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-IV). Almost half of the sample was found to be suffering from a psychiatric disorder (mostly anxiety and depression) when first interviewed, but after 3 months of not using pesticides, the rate of mental disorder had dropped by nearly 50% suggesting a strong association between mental health and exposure to pesticides. However, as this study used a pre/post exposure study design over a relatively short time frame, it is not possible to tell whether *long-term*, low-level exposure to OPs causes ill health; or how these symptoms may persist. Furthermore, participants with past episodes of acute toxicity may have been included in this study, as exposure screening only took into account the previous 12 months.

Another problem inherent in earlier work has been the failure to take account of possible confounding variables that may be involved in the aetiology of psychiatric symptoms when assessing exposed cohorts. For example, farming is a stressful and

physically demanding occupation and some researchers argue that socioeconomic and psychosocial factors are to blame for the elevated rates of psychological distress observed in this occupational group (Beard, Umbach, Hoppin, Richards, Alavanja, Blair, Sandler & Kamel, 2011; Deary, Willock, & McGregor, 1997; Pickett, King, Lees, Bienefeld, Morrison & Brison, 1998; Simkin, Hawton, Fagg & Malmerg, 1998). Previous research reporting associations between exposure to pesticides and psychiatric illness have often failed to take these issues into account, and lack detailed evaluations of participants' psychiatric history and background making it difficult to determine whether psychosocial or toxicological factors are involved in the aetiology of farmers' mental health complaints. What's more the effect of participants' physical health is rarely considered, despite poor-health being a risk factor for mood disorder result (NICE clinical guideline 91, 2009). Many studies simply compare rates of anxiety and depression in exposed and unexposed populations (e.g. Ames et al, 1995; Bazylewicz-Walczak et al. 1999; Farahat et al, 2003; Jamal et al, 2002; Reidy et al, 1992; Roldan-Tapia et al, 2006; Steenland et al, 2000; Stephens et al, 1995).

An exception is the work of Stallones and Beseler and colleagues (Stallones and Beseler, 2002a; 2002b; Beseler et al, 2006; 2008) in which the influence of demographic factors such as age, gender, marital status, alcohol use, health status and financial difficulties (known risk factors for depression) were explored in addition to pesticide exposure. They found higher rates of depression in individuals with a history of pesticide poisoning, even after adjustments were made for other risk factors. Pesticide poisoning was more strongly associated with depression than lower levels of exposure. However, they also found a relationship between high cumulative exposure

and depression in a subgroup of individuals who did not have a history of acute poisoning.

In 2010 we published the findings of a cross-sectional study of 127 UK sheep farmers which sought to determine the neurotoxicity of low-level exposure to OPs. We examined sheep farmers who had been repeatedly exposed to low levels of OPs during the process of sheep dipping (Mackenzie-Ross et al, 2010).

Neuropsychological assessment found exposed subjects performed significantly worse than matched controls and standardisation samples on tests of memory, response speed, fine motor control, mental flexibility and strategy making, even after controlling for covariates. In addition, more than 40% of study participants reported via questionnaire that they were suffering from significant levels of anxiety and depression compared to less than 23% of controls, but the true prevalence rate for these conditions, according to strict diagnostic criteria required further investigation.

In this paper we report findings from both self-report measures of mental health and the results of comprehensive clinical examinations in order to obtain a more accurate picture of the prevalence of psychological distress and psychiatric disorders amongst our cohort of sheep farmers. The aim of this study was two-fold: (1) to investigate whether farm workers with a history of low-level exposure to OPs report higher levels of psychological distress on subjective symptom questionnaires, compared to unexposed controls; (2) to investigate whether farm workers with a history of low-level exposure to OPs meet internationally agreed diagnostic criteria for a psychiatric disorder more often than unexposed controls, even after controlling for variables

known to effect mood (namely demographic and psychosocial factors, and physical health ratings).

2. Material and methods

2.1. Ethical Approval

Ethical Approval for this study was granted by the joint University College London (UCL) / UCL Hospital Committee A. Written informed consent was provided by all study participants.

2.2. Study Design and Participants

Details of the study design, recruitment method and population have been described previously (Mackenzie Ross et al, 2010). In summary, we evaluated neuropsychological and psychiatric functioning in 127 UK sheep farmers exposed to OP pesticides and 78 unexposed controls. Participants who were fit enough to be employed and participants who had retired on ill-health grounds were recruited into the study in order to take account of the potential ‘healthy worker’ effect. Attempts were made to match participants on demographic and geographic information, as well as working status and premorbid IQ (see section 3.1 below), in order to rule these variables out as potential confounds.

Recruitment of the exposed cohort involved writing to and telephoning farm owners from the North and South West regions of England, listed on relevant databases (e.g. UK National Business Directory, National Farmers Union membership lists, Wool Marketing Board lists). Recruitment of farmers who had retired on ill health grounds

was done by advertising as they were no longer listed in farming related databases. It was not possible to find a group of farmers in the UK who had no history of exposure to OPs making it necessary to identify an alternative occupational group that could act as a control. Rural police workers were chosen and were recruited by enlisting the help of local constabularies and the National Association of Retired Police Officers (NARPO) who contacted their members by email or newsletter to provide details of our study.

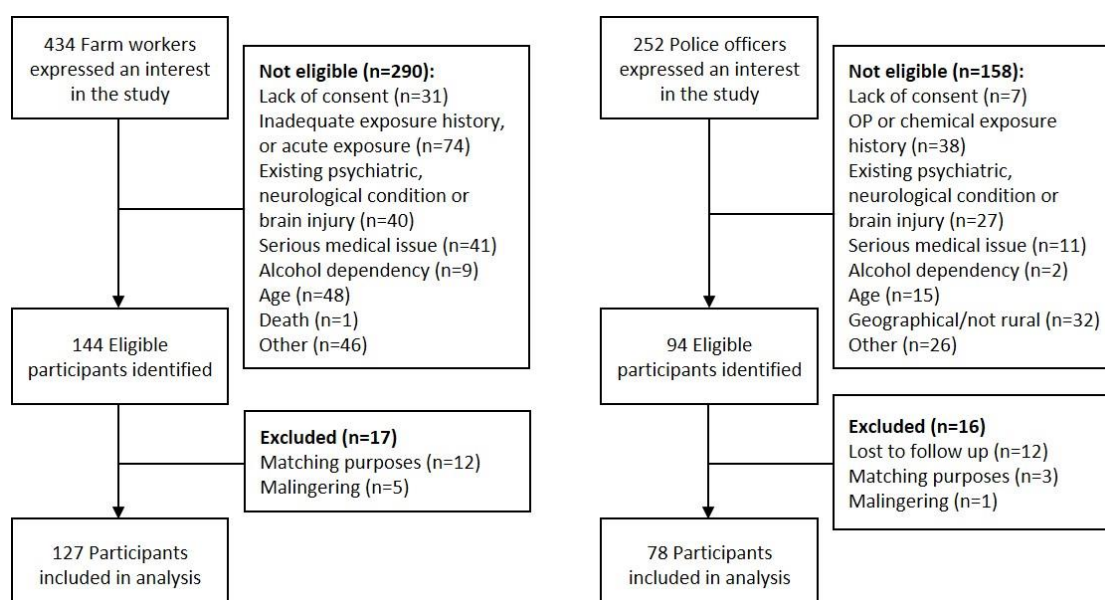


Figure 1 Participant flow diagram

Initially 434 farmers came forward and 252 police, however 67% of the farmers and 63% of the controls had to be excluded based on the inclusion/exclusion criteria, or lack of consent (see Figure 1). Individuals with a medical or psychiatric history that might otherwise account for their symptoms were excluded, as were individuals with a history of acute poisoning (sufficient to warrant medical attention) as the focus of our work concerned the neurotoxicity of low-level exposure to OPs (see Table 1 for

full inclusion and exclusion criteria). A further 12 farmers and 3 controls were excluded to in order to establish similar demographic profiles between the groups, and 12 controls were lost to follow-up. Finally, data were excluded from participants who showed evidence of poor effort/malingering on a psychometric test that is insensitive to severe brain injury but which is greatly affected by effort (Green, 2004).

Table 2 Inclusion and Exclusion Criteria.

	<i>Exposed cohort</i>	<i>Unexposed cohort</i>
<i>Inclusion</i>	<p>Aged between 18-70 years old</p> <p>Living in the South West or North of England.</p> <p>Exposure to organophosphate pesticides for a minimum of 5 years prior to 1991 (safety regulations were implemented in 1992).</p> <p>NO history of acute intoxication requiring medical intervention.</p>	<p>Aged between 18-70 years old</p> <p>Has worked in a rural area in the South West or North of England</p> <p>No known exposure to organophosphate pesticides.</p>
<i>Exclusion</i>	<p>History of psychiatric problems prior to exposure, neurological or serious medical problems which might otherwise account for any cognitive or emotional problems identified in this study.</p> <p>Substance abuse (including alcohol).</p> <p>Those with a history of acute organophosphate intoxication.</p>	<p>History of psychiatric problems, neurological or serious medical problems which might otherwise account for any cognitive or emotional problems identified in this study.</p> <p>Substance abuse (including alcohol).</p> <p>Exposure to organophosphates.</p>

2.3.Procedure and Measures

Study participants were visited at home or at their workplace and underwent an extensive psychological assessment and completed a number of questionnaires and measures to establish demographic, exposure, mood and health information.

2.3.1. Demographic and Exposure information

Demographic and exposure information was collected using a semi-structured interview. Farmers were asked to specify when they began working with OPs, in what capacity, their level of exposure in terms of frequency and duration, and whether they had a history of acute poisoning. The latter was defined as experiencing an incident in which they felt so unwell after exposure that they sought medical help.

2.3.2. Mental Health

The Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmond, 1983) was included to screen for symptoms of anxiety and depression. The HADS comprises 14 items, each scored from 0-3. Half of the items screen for anxiety, while the others relate to depression, allowing a score between 0-21 for each condition.

In addition, the Beck Anxiety (BAI; Beck & Steer, 1990) and Depression Inventories (BDI-II; Beck, Steer & Brown, 1996) were included as measures of symptom severity. Each scale contains 21 symptom-based items which participants respond to using a 0-3 Likert-type scale. Scores on each item are summed, producing a possible range of 0–63, with higher scores indicating more severe symptoms.

However, self-assessment scales are only valid for screening purposes and definitive diagnosis requires a comprehensive clinical examination, therefore, we also included a Structured Clinical Interview (SCID; First, Spitzer, Gibbon & Williams, 1996). Structured interviews provide an important method of standardising evaluations and improving diagnostic reliability and validity. The SCID was chosen for the current study because it was developed to standardise DSM-IV evaluations of psychiatric

disorders, and is considered the ‘gold standard’ for diagnosis. DSM-IV is a manual published by the American Psychiatric Association to assist clinicians in evaluating mental health disorders in both children and adults. The SCID aims to improve the reliability of DSM diagnoses and has been extensively validated (Rogers, 2001). Study participants were evaluated for the following: current major depressive episode and dysthymic disorder (which were combined to represent ‘depression’), and generalised anxiety disorder and panic disorder (which were combined to indicate ‘anxiety’).

2.3.3. Stressful Life Events

A Life Events Checklist (Holmes and Rahe, 1967) was included in an attempt to tease apart the relative contribution of recent stressful life events and exposure to pesticides in triggering mood disorder. This scale consists of 43 positive and negative life events such as divorce, marriage, retirement, change in financial state, which are capable of inducing stress and ill health. Each life event has an associated value according to how stressful they were considered to be by a standardisation sample of 394 individuals. Study participants were asked to state whether they had experienced any of these events over the last 12 months. Scores above 150 are associated with an increased risk of illness and a score above 300 is associated with a high risk of developing a stress related illness.

2.3.4. Physical health

Several studies report an association between physical health and depression, for example, individuals who suffer from chronic ill health and/or pain often suffer depression as a result (NICE, 2009). We therefore included two questions concerning

physical symptoms in our study to determine whether any elevated rates of mood disorder identified had arisen in response to physical ill health.

These were: (1) a generic measure of health status which was derived by asking participants to rate their overall health on a scale of 1 (meaning excellent) to 5 (indicating poor), and (2) a subjective measure of any pain they were in, ranging from 0 (meaning none) to 5 (indicating very severe).

2.4. Statistical Analyses

Participants' demographic information was explored using independent t-tests for continuous measures (age, years in education and premorbid IQ) and chi square for nominal data (gender and working status).

For self-report measures of mood, the effect of exposure was explored using Multivariate Analysis of Covariance, with unmatched demographic factors, physical health, pain and stressful life events scores entered as covariates. Independent t-tests and Mann-Whitney U tests were used to explore group differences in simple mood scores and covariates.

The relationship between SCID diagnoses and exposure group were explored using Binary Logistic Regression, with diagnosable depression or anxiety as outcome measures, and exposure group, age, physical health, pain and stressful life events scores entered as covariates.

3. Results

3.1 Demographic Information

Demographic characteristics of farmers and controls appear in Table 2. Farmers and controls were successfully matched for gender, education and premorbid IQ, but not age ($t(203)=2.40$, $p=.02$, $d=.35$). As such, age was entered into subsequent analysis as a covariate. Similar proportions of working and retired participants were in each group.

Table 2 Demographic, mood and covariate information for the control and exposed participants

	Exposed Group	Control Group
	Mean (SD)	Mean (SD)
Age*	54.73 (9.42)	51.73 (7.36)
Years in Education	11.57 (2.08)	11.95 (1.59)
Gender	102M, 25F	68M, 10F
Working Status	53% Working, 47% Retired	49% Working, 51% Retired
Matrix Reasoning	12.52 (2.53)	12.61 (2.19)
Stressful Life Events	76.62 (73.98)	85.23 (69.00)
Overall Health Rating**	3.17 (1.12)	2.55 (1.10)
Subjective Pain Rating	2.09 (1.30)	1.84 (1.17)
Lifetime Exposure (days)	80.78 (143.09)	N/A
BDI Score**	14.03 (10.96)	6.14 (5.72)
BAI Score**	9.04 (9.75)	3.43 (5.31)
HADS-D Score**	6.89 (4.61)	2.86 (2.58)
HADS-A Score**	7.52 (4.34)	4.41 (3.03)

* $p<.05$; ** $p<.001$

3.2 Exposure History

Farmers in this study had a history of low-level exposure to OPs over a number of years as a result of sheep dipping. The average number of years farmers spent

dipping sheep was 24.46 years (SD= 13.01) and farmers typically dipped twice a year for one day and for an average of about 7 hours per day. The mean time since farmers were last involved in dipping sheep was 10.31 years. A relatively simple estimate of ‘lifetime exposure’ was calculated by multiplying together the number of days per year farmers reported using OPs, by the number of years they spent using OPs. This can be seen in Table 2. Exposure history varied considerably despite participants appearing to have similar jobs.

3.3 Self-reported mood

Initial inspection of self-report mood measures indicated that the exposed cohort reported higher levels of anxiety (see Table 2). However, as all of these measures were significantly positively skewed, and displayed heterogeneous variances, they were all transformed using natural log transformation ($\ln(x_i+1)$). It is these scores that are analysed below.

3.3.1 Self-Reported Depression

A one-way independent MANCOVA, with transformed BDI and HADS-D scores as dependent variables, revealed that while stressful life events ($V=.08$, $F(2,179)=7.47$, $p=.001$, $\eta_p^2=.08$) and health rating ($V=.13$, $F(2,179)=13.59$, $p<.001$, $\eta_p^2=.13$) were significantly related to self-reported depression scores; age ($F<1$) and pain ratings ($V=.03$, $F(2,179)=2.39$, $p=.09$, $\eta_p^2=.03$) were not. After controlling for these variables, a significant main effect of Exposure Group on depression scores was found ($V=.14$, $F(2,179)=15.09$, $p<.001$, $\eta_p^2=.14$).

Follow-up univariate ANCOVAs, also controlling for the above covariates (summarized in Table 3) revealed that this main effect of exposure group on depression scores was driven by group differences on both BDI and HADS-D measures.

Table 3. Estimated marginal means for self-reported depression and anxiety scores (transformed) and associated covariate analyses.

Measure	Exposed			Control			Test	F	Partial Eta Squared
	N	Mean	SE	N	Mean	SE			
<i>Depression</i>							M	15.09***	0.14
BDI	117	2.30	0.08	70	1.7	0.1	A	20.15***	0.11
HADS-D	118	1.76	0.06	70	1.18	0.08	A	8.58***	0.14
<i>Anxiety</i>							M	16.38***	0.16
BAI	117	1.75	0.09	70	1.03	0.12	A	21.12***	0.11
HADS-A	118	1.97	0.06	70	1.48	0.07	A	26.61***	0.13

*** p<.001; A=ANCOVA, M=MANCOVA

3.3.2 Self-Reported Anxiety

A second one-way independent MANCOVA was conducted on transformed BAI and HADS-A scores. In this case, all covariates were significantly related to self-reported anxiety scores: stressful life events ($V=.09$, $F(2,179)=9.18$, $p<.001$, $\eta_p^2=.09$); health rating ($V=.07$, $F(2,179)=6.46$, $p<.005$, $\eta_p^2=.07$); pain rating ($V=.05$, $F(2,179)=4.51$, $p=.01$, $\eta_p^2=.05$); age ($V=.04$, $F(2,179)=3.45$, $p<.005$, $\eta_p^2=.04$). However, as with depression scores, even after controlling for these variables, a significant main effect of Exposure Group was found ($V=.15$, $F(2,179)=16.38$, $p<.001$, $\eta_p^2=.16$).

Again, follow-up ANCOVAs revealed that this effect of exposure group on self-reported anxiety was the result of group differences on both BAI and HADS-A measures.

3.4 Psychiatric Diagnosis

Frequency data concerning the rates of psychiatric diagnoses showed that levels of depression and anxiety were generally higher in the exposed cohort (13.9% and 21.7% respectively) than in the control group (depression = 5.3%; anxiety = 2.7%). While Fishers Exact Test revealed this difference to be significant for anxiety diagnoses ($p < .001$); this was not the case for depression ($p > .05$).

3.4.1 SCID Depression and Exposure

While no significant difference was found in the rates for depression cases, this was still followed up in order to investigate the relative contributions of the covariates to predicting depression. The different exposure groups were entered into a binary logistic regression with age, stressful life events, overall health and pain scores with depression diagnosis as the outcome.

The final model (containing all variables) was found to be statistically significant ($\chi^2(5, N=186)=23.30, p < .001$). The model explained between 11.8% (Cox and Snell R Square) and 23.3 % (Nagelkerke R Square) of the variance in depression diagnoses, and correctly classified 88.7% of cases. The variable beta values and associated Wald criterion can be seen in Table 4. In this case, exposure group was not found to significantly contribute to the model ($\chi^2=1.83, p=.18$) once the other covariates had been taken into account. In this case, the only significant predictor in the model was subjective health rating ($\chi^2=9.27, p=.002$) such that as health ratings increased in severity (by one unit), the likelihood of them being diagnosed with depression increased by a factor of 2.32.

3.4.2 SCID Anxiety and Exposure

To further investigate whether exposure group remained a significant predictor of anxiety cases when other possible covariates were taken into account, the same variables were entered into binary logistic regression with anxiety diagnosis as the outcome.

Table 4. Logistic Regression coefficients for predictors of psychiatric case classifications by SCIDs.

	B	S.E.	Wald	Sig.	Exp(B)
<i>SCID Anxiety</i>					
Constant	-3.13	1.45	4.66	0.031	0.044
Exposure Group	2.598	0.836	9.658	0.002	13.437
Age	-0.081	0.027	8.869	0.003	0.922
Stressful Life Events	0.003	0.003	0.705	0.401	1.003
Health Rating	0.489	0.258	3.591	0.058	1.631
Pain Rating	0.735	0.252	8.492	0.004	2.085
<i>SCID Depression</i>					
Constant	-2.105	1.829	1.325	.250	.122
Exposure Group	-.859	.635	1.830	.176	.423
Age	-.048	.028	2.954	.086	.953
Stressful Life Events	.001	.003	.138	.710	1.001
Health Rating	.842	.277	9.265	.002	2.322
Pain Rating	.294	.235	1.567	.211	1.341

All variables were entered into the model, which was found to be statistically significant ($\chi^2(5, N=184)=43.52, p<.001$). The model explained between 21.1% (Cox and Snell R Square) and 36.7 % (Nagelkerke R Square) of the variance in anxiety diagnoses, and correctly classified 85.9% of cases. The variable beta values and associated Wald criterion can be seen in Table 4. Importantly, exposure group was found to significantly contribute to the model ($\chi^2=9.66, p=.002$), along with age

($\chi^2=8.87$, $p=.003$) and pain rating ($\chi^2=8.49$, $p=.004$). The reported odds ratio demonstrated that participants in the exposure group were 13.44 times more likely than controls to be diagnosed with anxiety, even once the covariates had been taken into account.

4. Discussion

This study sought to determine whether farm workers with a history of low-level exposure to OPs are more vulnerable to psychiatric symptoms and mood disorder than unexposed controls. Several measures of emotional well-being were used including self-report measures and structured clinical interviews. Group comparisons based on self-report measures suggested long-term low-level exposure to OPs may be to blame for the elevated levels of anxiety and depression seen in the farming cohort as a significant effect of exposure group was found even after controlling for age and psychosocial risk factors such as ill-health, pain and stressful life events.

Demographic factors are unlikely to explain the elevated levels of distress seen in our cohort of farm workers as they were equivalent in both exposed and unexposed cohorts (except in the case of age, which was included as a covariate). However, this pattern of findings only held true for anxiety, when mood disorder was diagnosed using in-depth structured clinical interviews (with the SCID).

Binary logistic regressions attempted to establish the relative contribution of different risk factors to the diagnosis of depression and anxiety; and the results revealed potentially different aetiologies. While age, exposure and pain were all predictors of

anxiety diagnoses; depression was only predicted by subjective health ratings. So while participants in the exposed cohort may report more symptoms commonly associated with depression than controls (on both the BDI and HADS-D), they were not more likely to meet strict diagnostic criteria for a diagnosis of Major Depression (according to DSM-IV). Why this might be the case is unclear, but it is possible that self-report measures are not valid measures of psychiatric disorder for OP-exposed cohorts, possibly because many of the symptoms included in these questionnaires are non-specific and occur in a wide range of medical conditions (including several cognitive and somatic symptoms often reported following OP exposure). This notion is supported by a recent study which has found that the HADS and Beck Inventories may not be valid measures of psychiatric illness in OP-exposed participants (Harrison & Mackenzie Ross, under review); nor in many other patient groups with concurrent ill-health symptoms (e.g. Golden et al, 2007; Mitchell et al, 2010; Poole et al, 2006; Watson et al, 2014). Thus it is unclear how meaningful the information derived from self-report measures is in clinical, or real-world terms.

To date, only two studies from the USA have reported associations between low-level exposure and formally diagnosed psychiatric disorder in occupationally exposed cohorts. For example, Beseler et al (2008) evaluated the relationship between depression and pesticide exposure in 17,585 pesticide applicators enrolled in the AHS and found both acute high intensity and lower level exposures (in the absence of a history of acute poisoning) were associated with depression. More recently, Beard et al (2014) evaluated associations between mood disorder diagnosis and exposure to ten different classes of pesticides and fifty specific pesticides in 21,208 pesticide applicators, also in the AHS. They found that depression was associated with several

specific pesticides, including OPs, even after controlling for other risk factors.

Anxiety was not explored by either study.

While the results we obtained from self-reported measures support the findings of Beseler et al (2008) and Beard et al (2014), the findings we obtained using diagnostic interviewing was less supportive. There are a number of potential reasons for the discrepancies between our findings and those previously reported. First, the studies by Beseler et al (2008) and Beard et al (2014), both examined vast samples of participants greatly exceeding that seen in the current study, so it may be that the observed differences are simply due to differential power. However, there are also several other possibilities. For example, the exposure history of the cohorts used in these studies were markedly different from our own participants, which may have impacted on study findings. The cohort reported by Beseler et al (2008) had between 226 and over 752 days of exposure to pesticides which contrasts sharply with the exposure levels of the UK farmers who took part in the current study who reported an average of 80 days exposure. The comparison with Beard et al's (2014) cohort is less marked, as cumulative exposure in their cohort ranged from less than 56 days to more than 457 days. However, of interest is the fact that over half of the depressed individuals reported more than 226 days of exposure, almost triple our sheep farmers' average exposure. As such, it is possible that levels of exposure experienced by our cohort are less harmful in terms of psychiatric morbidity.

Indeed, as depression is often reported in acutely exposed individuals (for recent reviews see Freire and Koifman [2013] and Stallones and Beseler [2016]) it may be that only higher levels of exposure are associated with clinically significant

depressive symptoms; a notion that gains some support from the work of Beseler and colleagues who found pesticide poisoning is more strongly associated with depression than lower levels of exposure (Beseler et al, 2006; 2008). In contrast, anxiety (which has received markedly less attention in the literature) may be associated with low-level exposure to OPs. This is certainly something that warrants further investigation. Unfortunately, few researchers provide sufficient information about exposure history to allow a more detailed analysis of thresholds beyond which psychiatric problems may develop.

An additional reason for the discrepant findings could be the different methods used for establishing depression. The studies carried out by Beseler et al (2008) and Beard et al (2014) essentially involved asking participants a single question: whether or not they had ever been diagnosed with depression by a doctor. This is significantly different to the in-depth diagnostic interviews used in our study which assessed whether individuals met DSM-IV criteria for a diagnosis of anxiety disorder or major depression at the time of evaluation. It is possible that the incidence of depression is overestimated if the only measure of depression is a physician's diagnosis (which may even reflect a tendency for over-diagnosis of depression by GPs, e.g. see Dowrick & Frances, 2013). What's more, this type of measure provides no information regarding date of symptom onset and possible triggering factors.

Finally, the covariates examined in studies by Beseler et al (2008) and Beard et al (2014) did not take into account participant's subjective rating of their current physical health. While both studies included a frequency count of participants' visits to the doctor in the previous year (as a proxy measure of general health), and Beard et

al (2014) included an additional indicator of chronic ill-health (by using diabetes diagnoses as a covariate), it may be that it is the participant's actual *perception* of their health that is most important in predicting depression. This notion is supported by Stallones and Beseler (2002a), who found a significant relationship between depression and perception of poor health, in their study of 761 farm residents in Colorado. It may therefore be that the pattern of results reported by Beseler et al (2008) and Beard et al (2014) is actually a reflection of perceived deteriorating physical health, rather than exposure *per se*. Further research with the above AHS cohorts would need to be carried out to explore this possibility.

However, even if it is the case that perceived ill health is the main predictor of depression, that does not necessarily rule out OP exposure as a potential cause. It may just indicate that there is a relationship more complicated than dose-response at hand. For example, previous studies of UK sheep farmers (using methods ranging from postal questionnaires to clinical evaluations) have found that many individuals with a history of OP exposure complain of persistent ill health including subtle cognitive impairment, increased psychiatric morbidity, neurological abnormalities and chronic fatigue (Ahmed & Davies 1997; Beach, Spurgeon, Stephens, Heafield, Calvert, Levy & Harrington, 1996; Davies, Ahmed & Freer, 2000; Dunn, 2002; Jamal, Hansen & Julu, 2002; Mackenzie Ross et al, 2007; 2010; Pilkington, Buchanan, Jamal, Gillham, Hansen, Kidd, Hurley & Soutar, 2001; Solomon, Poole, Palmer, Peveler & Coggon 2007; Stephens et al, 1995; Tahmaz, Soutar & Cherrie, 2003). And more recently, several researchers have found a potential biological mechanism through which OP pesticides may cause ill health in some individuals. For example, paraoxonase (PON1) is a liver and plasma enzyme which contributes

significantly to the detoxification of OPs and two studies have found PON1 polymorphisms and low PON1 activity levels to be more common in people reporting ill health (Cherry et al, 2002; Mackness et al, 2003). In other words, people reporting ill health were less efficient at metabolising OP pesticides. As such, it is possible that those individuals who are less able to metabolise OPs, are more likely to develop ill health and are more likely to become depressed as a result, suggesting that the relationship between exposure and symptomatology is more complex than simple dose-response.

4.1 Limitations

As with most studies carried out in this area, there are several limitations that should be taken into account when interpreting the findings of this paper. First, while this study aimed to explore the impact of low-level exposure to OPs by excluding farmers with a history of pesticide poisoning, this was done by asking whether participants had ever sought medical help following exposure to OPs. As there is currently no single, agreed upon definition of what constitutes ‘acute’ or ‘low-level’ exposure to OPs, it is possible that the definition used in this study is not strict enough to accurately filter out all instances of acute exposure. For example, the more stoic and self-reliant attitudes that are often fostered in rural communities may result in reduced help-seeking behaviour (Jackson et al, 2007) resulting in individuals dealing with their ill-health symptoms alone. In addition, as participants were asked to report any poisoning incidents that had occurred over the entire span of their farming careers, there may have been errors in memory. Therefore, it is possible that this study inadvertently included participants with undiagnosed acute toxicity; and thus associations between exposure and ill health may be exaggerated.

In direct contrast, it is also possible that the study findings underestimate the risk associated with exposure to OPs, as more than 60% of potential participants had to be excluded from the study. Thus it may be the case that individuals with disabling disease who are particularly vulnerable to the neurotoxic effects of OPs were inadvertently excluded as a result of the strict inclusion/exclusion criteria used. Future research investigating individual differences in the ability to metabolise OPs may be able to shed further light on this issue.

5. Conclusions

Previous research suggests that individuals with a prior history of pesticide poisoning are at increased risk of psychiatric disorder (Freire & Koifman, 2013), but findings regarding the impact of cumulative low-level exposure are less clear. In the present study we found UK sheep farmers with a history of low-level exposure to OPs were more likely to report symptoms of anxiety and depression than unexposed controls, even after controlling for demographic and psychosocial risk factors for these conditions. However, this was only true when self-report measures were used (the BDI-II, BAI and HADS). When more in-depth structured clinical interviews were used for diagnoses, exposure was only related to anxiety disorder, and not depression. These findings have implications for future studies as self-report measures may overestimate the incidence of anxiety and depression, lack ecological validity, and potentially exaggerate the impact of exposure on psychological well-being and psychiatric illness in occupational groups exposed to potentially neurotoxic substances such as pesticides.

In addition, this study found that perceived ill health was the primary predictor of depression diagnosis and identified several other predictors of anxiety. As such, future research may need to carry out more detailed evaluations of mental health, including assessment of known demographic and psychosocial risk factors associated with mental illness, and measures of participant's perceived health, before causal relationships with low-level pesticide exposure are assumed. Prospective, longitudinal studies offer the best chance of getting a definitive answer to the question of whether low-level exposure to OPs causes neuropsychiatric damage.

Conflict of Interest

The authors have no conflict of interest to declare.

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